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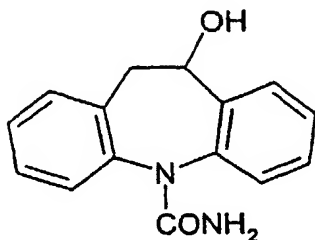
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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: MONOHYDROXYCARBAMAZEPINE FOR USE IN THE PREPARATION OF A MEDICAMENT FOR THE TREATMENT OF AFFECTIVE AND ATTENTION DISORDER AND NEUROPATHIC PAIN



(I)

(57) Abstract: The invention relates to the use of a carbamazepine derivative of the Formula (I) for the treatment of affective and attention disorders, neuropathic pain and neuropathic pain related disorders.

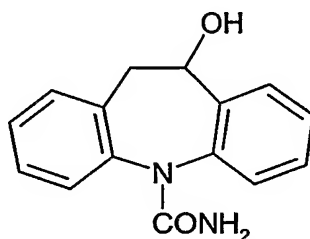
WO 03/042182 A1

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MONOHYDROXYCARBAMAZEPINE FOR USE IN THE PREPARATION OF A MEDICAMENT FOR THE TREATMENT OF AFFECTIVE AND ATTENTION DISORDER AND NEUROPATHIC PAIN

The present invention relates to new pharmaceutical uses of a carbamazepine derivative.

More particularly the present invention relates to new pharmaceutical uses for monohydroxycarbamazepine of formula I



I

Monohydroxycarbamazepine (10-hydroxy-10,11-dihydro-carbamazepine), the main metabolite of the antiepileptic oxcarbazepine (Trileptal<sup>®</sup>) is well known from the literature [see for example Schuetz H. et al., *Xenobiotica* (GB), 16(8), 769-778 (1986)] and can be prepared synthetically starting from oxcarbazepine according to conventional methods. Monohydroxycarbamazepine has been first disclosed in GB 1310120. The compound is indicated to be suitable for the treatment of psychosomatic disturbances, epilepsy, trigeminal neuralgia and cerebral spasticity.

In accordance with the present invention, it has now surprisingly been found that the compound of formula I is useful in the treatment of affective and attention disorders including e.g. depression and bipolar mood disorders; as well as neuropathic pain and related disorders.

The activity of the compound of formula I in the treatment of affective and attention disorders and of neuropathic pain is evidenced, for example, by its ability to inhibit gamma-aminobutyric acid (GABA) turnover. This is due to feedback inhibition caused by the activating effect of these compounds on GABA transmission.

The role of GABA in bipolar and other mood disorders is unquestioned and topic of several reviews (e.g., Emrich et al. Effect of sodium valproate on mania. The GABA-hypothesis of affective disorders. *Arch. Psychiatr. Nervenkr.* 1980; 229:1-16; Petty. GABA and mood disorders: a brief review and hypothesis. *J. Affect. Disord.* 1995; 34:275-81). Drugs effective

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in (bipolar) mood disorders and also in anxiety and depression, e.g. lithium, valproate and diazepam are known to inhibit the GABA turnover rate. This is due to feedback inhibition caused by the activating effect of these compounds on GABA transmission.

Also, the role of GABA in chronic pain is unquestioned and topic of several reviews (e.g., Stamford. Descending control of pain. Br. J. Anaesth. 1995; 75:217-21). Drugs effective in chronic pain such as valproate are known to inhibit the GABA turnover rate. This is due to feedback inhibition caused by the activating effect of these compounds on GABA transmission.

The activity of the compound of formula I on GABA turnover is evidenced in the following experiment:

The determination of GABA turnover is based on the linear increase in GABA level observed after the maximal inhibition of gamma- aminobutyric acid transaminase (GABA-T). The values obtained with this approach for the rate of GABA synthesis are independent of the inhibitors used and within the catalytic capacity of the enzymes involved in the GABA shunt.

Under these conditions, the compound of formula I dose-dependently inhibits the GABA turnover rate at doses of 30 to about 300 mg/kg p.o.

The activity of the compound of formula I in the treatment of affective and attention disorders treatment is also evidenced, for example, in tests suitable for detecting drugs having potential behavioural desinhibitory and/or sociotropic effects which are thought to be relevant for recovery from social withdrawal, a cardinal feature of depression and related psychiatric conditions. For instance, drug effects on social withdrawal of intruder mice can be evaluated by using the basic method as described in Triangle, 1982, 21:95-105 and J. Clin. Psychiatry, 1994, 55:9 (suppl. B) 4-7.

Within the dose range of 1 to about 100 mg/kg p.o., the compound of formula I increases social investigation in the treated mouse under such experimental conditions.

In view of its anxiolytic-/antidepressant- like stimulating effect on GABA transmission and sociotropic activity, the compound of formula I is useful in the treatment of affective disorders

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including depression and bipolar disorders, e.g. manic-depressive psychoses, extreme psychotic states e.g. mania, schizophrenia, and excessive mood swings where behavioural stabilization is desired. In addition, the compound is indicated in ADHD (attention deficit hyperactivity disorders) and other attention disorders, e.g. autism, (and) in anxiety states, generalized anxiety and agoraphobia, as well as those behavioural states characterized by social withdrawal e.g. negative symptoms.

The direct activity of the compound of formula I in the treatment of neuropathic pain is evidenced, for example, in the following model of neuropathic pain in the guinea pig:

Dunkin Hartley guinea pigs are anaesthetised with enflurane (in N<sub>2</sub>O:O<sub>2</sub> for guinea pigs) and the left sciatic nerve is exposed and partially ligated with thread. This procedure produces a mechanical hyperalgesia, which develops within 2-3 days and is maintained for at least 4 weeks. Paw withdrawal thresholds to a pressure stimulus are measured using an analgesymeter. Mechanical thresholds are taken on both the ipsilateral (ligated) and contralateral (unligated) paw prior to and then up to 6 hours following drug or vehicle administration. Reversal of hyperalgesia at each time point is calculated. Groups of 6 animals are used. Statistical analysis is carried out on withdrawal threshold readings using ANOVA followed by Tukey's HSD test.

In this model, the compound of formula I significantly and dose-dependently reverses neuropathic mechanical hyperalgesia at doses of 10 to about 100 mg/kg p.o. and 3 to about 100 mg/kg s.c.

The activity of the compound of formula I in the treatment of neuropathic pain and related disorders can be confirmed in clinical trials evaluating the efficacy of a compound in treating chronic pain in patients with diabetic neuropathy.

In such studies, the compound of formula I is found to decrease pain severity ratings relative to placebo during the Maintenance and Follow-up Periods, in a statistical significant way.

The compound of formula I is therefore useful in the treatment of neuropathic pain and associated hyperalgesia, including trigeminal and herpetic neuralgia, diabetic neuropathic

pain, migraine, causalgia and deafferentation syndromes such as brachial plexus avulsion, and in spasticity and related disorders.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.05 to about 150, preferably from about 0.1 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 0.5 to about 5000, preferably from about 1 to about 500mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form, for example once a day.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The agents of the invention can be administered in vivo either alone or in combination with other pharmaceutical agents, e.g. agents effective in the treatment of diseases and conditions in which the human VR1 activation plays a role or is implicated including cyclooxygenase-2 (COX-2) inhibitors, such as specific COX-2 inhibitors (e.g. celecoxib, COX189, and rofecoxib) or in general nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. acetylsalicylic acid, propionic acid derivatives), tricyclic antidepressants (e.g. Anafranil®, Asendin®, Aventyl®, Elavil®, Endep®, Norfranil®, Norpramin®, Pamelor®, Sinequan®, Surmontil®, Tipramine®, Tofranil®, Vivactil®, Tofranil-PM®), anticonvulsants (e.g. gabapentin), GABA<sub>B</sub> agonists (e.g. L-baclofen), opioids, Vanilloid receptor antagonists and Cannabinoid (CB) receptor agonists, e.g. CB<sub>1</sub> receptor agonists.

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners, according to the invention can be prepared in a manner known per se and are thus suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination

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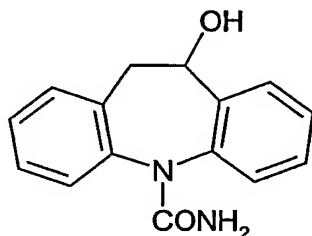
with one or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application.

The invention further provides the use of the compound of formula I for the manufacture of a pharmaceutical composition for the treatment of affective and attention disorders, neuropathic pain and neurophatic pain related disorders.

The invention furthermore provides a method for the treatment of affective and attention disorders, neuropathic pain and neurophatic pain related disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of the compound of formula I.

Claims:

1. The use of monohydroxycarbamazepine of formula I



I

for the treatment of affective and attention disorders, neuropathic pain and neurophatic pain related disorders.

2. A pharmaceutical composition comprising the compound of formula I according to claim 1, in association with at least one pharmaceutical carrier or diluent, for use in the treatment of affective and attention disorders, neurophatic pain and neurophatic pain related disorders.
3. The use of the compound of formula I according to claim 1, for the manufacture of a pharmaceutical composition for the treatment of affective and attention disorders, neurophatic pain and neurophatic pain related disorders.
4. A method for the treatment of affective and attention disorders, neurophatic pain and neurophatic pain related disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of the compound of formula I according to claim 1.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/12578

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D223/28 A61K31/55 A61P25/24

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 310 120 A (CIBA GEIGY AG) 14 March 1973 (1973-03-14) cited in the application claims; examples	1-4
X	----- CZUCZWAR S J ET AL: "THE NEW GENERATION OF GABA ENHANCERS POTENTIAL IN THE TREATMENT OF EPILEPSY" CNS DRUGS, ADIS INTERNATIONAL, AUCKLAND, NZ, vol. 15, no. 5, 2001, pages 339-350, XP001095132 ISSN: 1172-7047 page 340 -page 348 -----	1-4



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

17 December 2002

Date of mailing of the international search report

14/01/2003

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 02/12578

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 1,4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International Application No

PCT/EP 02/12578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1310120	A	14-03-1973	
		CH 505101 A	31-03-1971
		AT 294106 B	10-11-1971
		BE 747086 A1	09-09-1970
		BG 17600 A3	10-11-1973
		CA 920587 A1	06-02-1973
		CS 154295 B2	29-03-1974
		DE 2011045 A1	08-10-1970
		DK 133898 B	09-08-1976
		ES 377280 A1	16-06-1972
		FI 50524 B	31-12-1975
		FR 2035999 A5	24-12-1970
		IE 34050 B1	22-01-1975
		IL 34027 A	29-12-1972
		NL 7003026 A ,C	02-10-1970
		NO 131546 B	10-03-1975
		NO 131546 C	25-06-1975
		PL 80544 B1	30-08-1975
		SE 354069 B	26-02-1973
		YU 53770 A ,B	31-12-1977